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REVIEW

Long-Acting Injectable Antipsychotics in Schizophrenia: Literature Review and Practical Perspective, with a Focus on Aripiprazole Once-Monthly

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ABSTRACT

Introduction: Prevention of relapse is a major challenge in schizophrenia, a disease characterized by poor adherence to antipsychotic medication leading to multiple rehospitalizations and a substantial burden-of-care.
Methods: We narratively review published clinical data from the development of long-acting injectable (LAI) formulations of antipsychotic drugs and examine the comparative effectiveness of oral versus LAIs in schizophrenia, with a focus on the second-generation LAI antipsychotic aripiprazole. Evidence is presented from studies with naturalistic/pragmatic as well as explanatory trial designs, supported by the clinical experience of the authors.
Results: LAI formulations of antipsychotic drugs offer advantages over oral medications and there is good evidence for their use as a first-choice treatment and in younger patients. Key phase III studies have shown aripiprazole once-monthly 400 mg (AOM 400) to be effective and well tolerated, with high rates of adherence and low rates of impending relapse. In a recent randomized trial with a "naturalistic" study design more representative of routine clinical practice, AOM 400 was well tolerated and had significantly greater effectiveness than paliperidone LAI overall and in younger patients aged ≤35 years.
Conclusion: Results across the "full spectrum" of efficacy in traditional clinical trials as well as those encompassing the concept of effectiveness in a more naturalistic setting of real-life clinical practice support the use of AOM 400 as a valid long-term treatment option in schizophrenia overall, as well as earlier in the treatment course, and not solely in situations of poor adherence or when oral antipsychotics have failed.

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INTRODUCTION

Schizophrenia is a pervasive and disabling psychotic chronic condition with a major burden on patients, their families, and society [1, 2]. During their lifetime, about 1% of the world population will develop schizophrenia, typically preceded by prodromal symptoms of psychosis leading to a first psychotic episode and starting in young adulthood, although the distressing condition can occur at any age [2, 3]. Individuals with schizophrenia have a shorter life expectancy than the general population, with an increased risk of physical illness, especially cardiovascular disease, as well as higher rates of suicide and accidental injury [2, 4–6]. The long-term course of schizophrenia is marked by episodes of partial or full remission broken by relapses, while social and occupational functioning, quality of life and ability to live an independent life are constrained, and there is an increased risk of substance abuse, suicide and violent behavior, especially during the period of relapse [2, 7].

While the prevention of relapse, accompanied by delusions, which may potentially cause harm to the patient and their societal contacts, hallucinations, and disorganized speech and behavior, is a major challenge in schizophrenia, the disease is also characterized by poor adherence to antipsychotic medication leading to a need for multiple rehospitalizations and a substantial direct and indirect cost burden [2, 8–12].

In this narrative review, we examine published clinical data from the development of long-acting injectable (LAI) formulations of antipsychotic drugs and review the evidence for the comparative effectiveness of oral versus long-acting antipsychotics in the management of schizophrenia, with a focus on the second-generation antipsychotic LAI aripiprazole. Evidence from studies with naturalistic/pragmatic as well as explanatory trial designs is presented, supported by the clinical experience of the authors.

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Treatment of Schizophrenia: Ensure the Continuity of Therapy

The development and introduction of antipsychotic drugs significantly improved treatment outcomes and quality of life for patients with schizophrenia, and there is general acceptance of their valuable contribution at all stages of schizophrenia [2, 13–17]. Although an in-depth discussion of all therapeutic options for patients with schizophrenia is beyond the scope of this article, it is clear that all patients affected by schizophrenia will require long-term treatment. Long-term pharmacological therapy in the stable or maintenance phase should be individually tailored to the needs and preferences of the patient and directed at ensuring symptom remission and control of relapses; moreover, the patient's level of psychosocial functioning, independence and quality of life is maintained or improved by long-term therapy, while the monitoring for adherence and adverse effects of treatment is continued [4, 14, 18].

Antipsychotic pharmacological therapy should be accompanied by psychoeducational and psychosocial interventions customized to the patient, including occupational therapy, community-based treatment, family interventions, vocational rehabilitation and, when appropriate, counseling and psychotherapy, behavior therapy, and cognitive behavioral therapy (CBT) [2, 13–15, 17]. UK guidelines recommend CBT as first-line therapy in at-risk adult populations [2].

Effective antipsychotic medications, in particular long-acting injectable (LAI) formulations, facilitate and support the patient's ability to benefit from interventions designed to encourage successful rehabilitation and re-entry into society [14].

Assuring continuity of treatment is essential to the prevention of relapse, a key focus in the treatment of schizophrenia. Therefore, therapeutic interventions that enhance treatment adherence, such as LAIs, are a clinical priority within the treatment plan. Data from a systematic review and meta-analysis show a weighted 1-year relapse rate of 77% in patients with a first episode of schizophrenia who

discontinue antipsychotic therapy, increasing to over 90% at 2 years, compared with a mean relapse risk of 3% in those continuously treated with antipsychotics [19]. Similarly, patients completely adherent to their antipsychotic medication are at significantly reduced risk of hospitalization or emergency room visits for a mental health reason [20]. It is also becoming clear that early intervention in patients with psychosis has a beneficial effect on long-term outcomes, while, conversely, delaying access to effective mental health services may slow or prevent complete recovery, increase the risk of relapse and lead to poor long-term clinical and social outcomes [21]. Continuity of treatment from the early stages of the disease may, indeed, significantly reduce the risk of recurrence and improve patient outcomes [22].

Antipsychotic drugs with LAI formulations were developed to reduce the problem of non-adherence, which is estimated to be as high as 40% or more [10, 14, 23]. LAI antipsychotics have a number of advantages over oral antipsychotics. LAIs are formulated to maintain stable therapeutic blood levels during the period between injections (commonly every 2–4 weeks, with the exception of a new formulation of paliperidone palmitate administered every 3 months), reduce the need to remind patients to take their medication, lack an abrupt decline in blood level of the antipsychotic agent if an injection is missed, avoid bioavailability issues that occur with oral preparations (gastrointestinal absorption problems and hepatic first-pass metabolism), and reduce the risk of accidental or deliberate overdose [2, 14]. Furthermore, LAIs facilitate the regular contact between patients and physician essential for effective monitoring of the patient's progress, allow physicians to rule out non-adherence as a cause of relapse, and, should a patient miss an injection, there remains some time to act to avert a crisis [24]. However, potential disadvantages include reduced flexibility of administration, a potentially extended period of titration to optimal dose, and a longer duration required to achieve steady state, relative to oral administration [25].

Long-acting formulations of second-generation antipsychotic drugs, including risperidone, olanzapine, paliperidone and aripiprazole, have been developed [25]. They provide physicians with the opportunity of rapidly achieving steady state of the antipsychotic agent, together with good flexibility in available dosages. For example, aripiprazole is available in a long-acting formulation for administration once-monthly at dosage of 400 mg.

Determining the appropriate duration of antipsychotic therapy to ensure long-term continuity of the maintenance phase of schizophrenia is the subject of some debate. There is evidence that, compared with continuing treatment, there is a higher risk of relapse if treatment is discontinued in patients despite their being stable on antipsychotics for up to 5 years after an acute episode [26]. Therefore, treatment guidelines such as those of the Canadian Psychiatric Association and the World Federation of Societies of Biological Psychiatry (WFSBP) recommend continuation of antipsychotic drugs for the treatment of first-episode psychosis for at least 2 years after first remission, with a minimum of 5 years of relapse-free stability before considering slow withdrawal of antipsychotic drugs over an extended period (6–24 months) in patients with a history of recurrences [27, 28]. However, as with long-term therapy for any chronic disease, careful consideration of treatment-related side effects must be undertaken. First-generation, or typical, antipsychotic agents are associated with significant and potentially disabling and distressing side effects, including extrapyramidal side effects (parkinsonism, dystonia, akathisia, tardive dyskinesia), lethargy, sedation and weight gain [2]. Newer atypical or second-generation antipsychotics were developed to be more effective while reducing the likelihood of disabling side effects. In particular, they have a lower risk of acute extrapyramidal symptoms and tardive dyskinesia, although they may be associated with other side effects, such as weight gain, hyperprolactinemia and metabolic effects [2].

Although LAI antipsychotics have often been chosen only when oral formulations had failed, and many clinicians adopt the position that LAI antipsychotic agents should not be used as first-line therapy for schizophrenia, there is

good evidence for their use as a first-choice treatment, supported by recent guidelines and studies [14, 29]. A recent large 'real-world' cohort study of the use of oral and LAI antipsychotics after the first hospitalization of patients for schizophrenia found that less than half [45.7%, 95% confidence interval (CI) 43.7–47.6%] adhered to their discharge antipsychotic during the first 60 days after discharge [29]. However, there was a significantly lower risk of all-cause antipsychotic discontinuation with LAIs, and LAIs significantly reduced the risk of rehospitalization, compared with oral antipsychotics. During a mean follow-up of 2 years, the adjusted hazard ratio (HR) for rehospitalization for LAIs was about a third that associated with oral antipsychotics (HR 0.36, 95% CI 0.17–0.75, $P = 0.007$) [29], indicating that LAIs were associated with substantially better outcomes. Indeed, the Texas Medication Algorithm Program, following expert panel review of the clinical evidence for the treatment of schizophrenia, recommends that physicians should assess and consider the use of LAIs when schizophrenic patients are inadequately adherent at any stage [30, 31]. Furthermore, the French Association for Biological Psychiatry and Neuropsychopharmacology guidelines for the use and management of antipsychotic depots in clinical practice recommend LAI antipsychotics be considered as first-line treatment in the majority of patients who require long-term therapy [32].

The concept of 'effectiveness', that is, a comprehensive pragmatic approach that integrates aspects of efficacy, safety and tolerability from the perspective of both patient and clinician, is essential to the satisfactory evaluation of a long-term treatment [33, 34]. The comparative effectiveness of oral versus long-acting antipsychotics has been addressed in a number of studies, reviewed recently by Alphs et al. [35], with inconsistent findings, and by Suzuki, who places comparisons between oral and long-acting antipsychotics in a clinical context, commenting that results from randomized comparative trials rely heavily on study design and population [36]. These inconsistent findings may be influenced by methodological considerations in clinical study design; that is, naturalistic/pragmatic versus explanatory trial designs. Explanatory clinical trials are designed to measure the efficacy of a treatment in a relatively homogeneous patient population under highly controlled and well-defined conditions of frequent, intensive, and standardized clinical assessments that make adherence to treatment more likely than in routine clinical practice [35]. Such trials are unlikely to recruit patients at added risk of non-adherence, e.g., patients with first-episode psychosis or substance abuse disorders, or those with a history of violence. In contrast, pragmatic trials measure the effectiveness of an intervention in a more heterogeneous patient population better representative of a more naturalistic clinical practice setting. Indeed, two large meta-analyses of randomized controlled trials, which concluded that there is no advantage of LAIs over oral antipsychotics in preventing relapse and hospitalization [37, 38], were largely dependent on highly explanatory trials, whereas meta-analyses that have included trials with more pragmatic trial designs have shown significant advantages for LAI formulations over oral antipsychotic in the naturalistic setting [39–41]. LAI formulations have been consistently superior to oral antipsychotics in mirror-image studies which compare treatment periods with oral antipsychotics with those of LAIs in the same patients. Results from a recent systematic review and meta-analysis of mirror-image studies showed strong superiority of LAIs compared with oral antipsychotics in preventing hospitalization in patients with schizophrenia [42].

Despite evidence that LAI antipsychotics are highly efficacious in schizophrenia, and some real-world evidence suggesting that prescribed LAI antipsychotics are often used concomitantly with oral antipsychotics and psychotropics [43], LAI antipsychotics remain an underutilized treatment option.

In fact, there is research to show that underutilization of LAIs originates more from ideologic hesitation and attitudinal barriers on the part of psychiatrists and physicians rather than on any skepticism from patients towards LAI drugs [44–48], and there is increasing acceptance that psychiatrists should consider the use of LAIs as a treatment option more often

in general, and also earlier in the treatment course [49].

Aripiprazole Long-Acting Injectable in Schizophrenia

Aripiprazole is a second-generation antipsychotic. Unlike other currently available first- and second-generation antipsychotics, the antipsychotic efficacy of aripiprazole has been mainly attributed to a combination of partial agonism at human dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors [50–53]. Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors, moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, α_1-adrenergic and histamine H_1 receptors, and moderate affinity for the serotonin reuptake site [54]. Consequently, aripiprazole has a low potential for clinically relevant weight gain, sedation, or metabolic adverse events [54–58].

Aripiprazole is well absorbed and widely distributed throughout the body [54]. Compared with Cmax of the tablet formulation, geometric mean maximum concentration is higher (mean 19%) with aripiprazole 5 mg short-acting intramuscular (IM) administration [59]. Systemic exposure is generally similar after aripiprazole IM injection and after oral tablet administration, over 24 h, and the IM route of administration is not expected to alter aripiprazole metabolic pathways [59]. Aripiprazole dose is to be reduced with concomitant administration of potent CYP3A4 or CYP2D6 inhibitors and should aripiprazole be given concomitantly with potent CYP3A4 inducers, aripiprazole dose is to be increased [54].

An extended release formulation of aripiprazole [Abilify Maintena®; aripiprazole 400 mg once-monthly (AOM 400)] has been developed [60]. AOM 400 and 300 are both approved in Europe for maintenance therapy of schizophrenia in adult patients stabilized with oral aripiprazole. The formulation is a powder to be reconstituted in sterile water for IM injection in the gluteal or deltoid muscle [60]. The pharmacokinetics, tolerability and safety of aripiprazole once-monthly were investigated in a 24-week, open-label, parallel arm pharmacokinetic study that established a recommended dose of 400 mg [61], both as first and maintenance dose. AOM 400 provided sustained mean plasma concentrations of aripiprazole comparable to those achieved with multiple consecutive daily doses of oral aripiprazole 10–30 mg/day at steady state, without any clinically meaningful changes in adverse events, laboratory values, vital signs, or electrocardiogram measurements [61].

The recommended maintenance dose of AOM, 400 mg, can be reduced to 300 mg in the advent of adverse events or in patients who are known to be cytochrome P450 (CYP) 2D6 poor metabolizers. Patients taking AOM 400 concomitantly with strong CYP3A4 (e.g., ketoconazole, itraconazole) or strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, quinidine) for more than 14 days also require a dose reduction to 300 mg [60]. Concomitant administration of AOM in patients taking CYP3A4 inducers (e.g., carbamazepine, rifampicin, phenobarbital) for more than 14 days is forbidden.

The registrational trials for AOM 400 consisted of two pivotal international randomized, double blind, multicenter, phase III studies that compared AOM 400 either with placebo [55] or with active and sub-therapeutic threshold treatments [62] in adults aged 18–-60 years meeting DSM-IV-TR schizophrenia criteria and requiring maintenance antipsychotic therapy. Time to impending relapse (the primary endpoint) was significantly delayed with AOM 400 relative to placebo [55], while AOM 400 was non-inferior to oral aripiprazole (10–30 mg) and superior to a subtherapeutic dose (50 mg) of once-monthly aripiprazole, for the primary endpoint of impending relapse rate [62]. AOM 400 was shown to be well tolerated in both studies, with minimal injection site pain and a safety profile consistent with comparators and with that reported for oral aripiprazole in previous registrational maintenance studies [55, 62].

In the placebo-controlled study, as well as significantly delaying time to impending relapse compared with placebo, AOM 400 reduced relapse rates, with 39.6% of placebo

recipients meeting criteria for relapse at the 52-week final analysis, compared with 10.0% of AOM 400 recipients (HR 5.03, 95% CI 3.15–8.02) [55]. Mean positive and negative syndrome scale (PANSS) total scores improved from a mean of 65.1 during the oral aripiprazole and AOM stabilization phases, and were similar in both groups at the double blind baseline (54.4 for placebo and 54.5 for AOM 400). In patients randomized to AOM 400, the improvements in PANSS total scores were maintained throughout the 52-week treatment period (mean change of +1.4), while significant increases in mean PANSS total scores were observed in the placebo group from as early as week 2 and continued at all time points (+11.6 at week 52, $P < 0.0001$). As the efficacy of AOM 400 was demonstrated at the preplanned interim analysis, the study was terminated early to avoid further exposure to placebo.

In the active-controlled non-inferiority study, PANSS total scores deteriorated in the aripiprazole once-monthly 50-mg group during the treatment phase, and there were statistically significant differences for AOM 400 versus both aripiprazole once-monthly 50 mg and oral aripiprazole at week 38 (study end). At week 38, the change from baseline in PANSS total score was –1.66 for AOM 400, +0.58 for oral aripiprazole, and +3.08 for aripiprazole once-monthly 50 mg ($P = 0.0272$ for AOM 400 vs. oral aripiprazole and $P = 0.0002$ for AOM 400 vs. aripiprazole once-monthly 50 mg) [62].

In these and other key phase III studies, 90% of patients across studies who were initiated on the AOM 400 mg dose remained on that dose throughout, and rates of discontinuation due to lack of efficacy were in the order of 2%–10% [55, 62–64]. As well as confirming 400 mg as an effective, safe and well tolerated initial dose in schizophrenic patients, Raoufinia et al. demonstrated that the efficacy, safety and tolerability of AOM 400 in patients who were stabilized with oral aripiprazole for 2 weeks after the 1st injection of once-monthly aripiprazole was consistent regardless of whether patients were previously stabilized on oral aripiprazole 10 or 30 mg/day [64]. Overall, the pivotal studies have shown that AOM 400 produces an effective therapeutic effect over extended periods of up to 52 weeks.

In a naturalistic study in a community setting, switching patients from oral antipsychotics to AOM 400 significantly reduced hospitalization rates (2.7% vs. 27.1% at 3 months and 8.8% vs. 38.1% at 6 months, $P < 0.0001$) [56]. This supports evidence from a meta-analysis showing that LAIs are more effective in reducing the rates of hospitalization of patients with schizophrenia than oral antipsychotics [65].

The QUAlity of LIfe with AbiliFY Maintena® (QUALIFY) study [57] is one of a very limited number of randomized studies designed as a head-to-head comparison of the effects of two second-generation LAI antipsychotics with different mechanisms of action on health-related quality of life and functioning. In this study, AOM 400 was compared with paliperidone palmitate once monthly. In contrast to more traditional pivotal studies, the QUALIFY study design integrated "pragmatic" or "naturalistic" features, more similar to real-life clinical practice settings. Rather than assessing affectivity and cognition as primary outcomes, the chosen primary endpoint was change in the Heinrichs–Carpenter Quality-of-Life Scale (QLS), a health-related quality-of-life scale that assesses intrapsychic, social, and negative symptoms and their consequences for functioning in schizophrenia [60] This endpoint reflects a key long-term aim of antipsychotic therapy. The QLS consists of 21 items in 4 domains consisting of Interpersonal Relationships (8 items), Instrumental Role (4 items), Intraphysic Foundations (7 items), and Common Objects and Activities (2 items) [66]. Items are rated on a 7-point scale for 0 (severe impairment) to 6 (normal/unimpaired functioning) with a total score between 0 and 126; a higher score indicates better quality of life and/or functioning. A difference of 5.3 points on the QLS total score is considered to be clinically meaningful [67]. The effects of treatment on clinical symptoms were evaluated using the CGI-S scale, which provides the physician's impression of the current state of mental illness of the patient on a 7-point scale (from 1, normal/not at all ill) to 7 (extremely ill) [57].

QUALIFY was a 28-week, randomized, non-inferiority, open-label, rater-blinded, head-to-head study that comprised oral conversion to IM injection of AOM 400 or paliperidone palmitate treatment [flexible dosing, per label, 50–150 mg of paliperidone per month (EU and Canada) or 78–234 mg of paliperidone palmitate per month (US)] and continuation of IM injections every 4 weeks. A total of 295 patients were randomized to treatment, and 183 patients (68% of the AOM group and 57% of the paliperidone once-monthly group) completed the study. The primary endpoint was designed to determine non-inferiority and superiority based on change in QLS total score from baseline to week 28, utilizing a mixed model for repeated measurements. The non-inferiority criterion was met if the lower bound of the two-sided 95% CI was greater than −5 (non-inferiority margin) for the least squares mean (LSM) treatment difference in change in QLS from baseline at week 28 for AOM 400 versus paliperidone palmitate. If met, a predefined test of superiority was to be conducted. Superiority of AOM 400 over paliperidone palmitate was taken to be confirmed if the lower bound of the two-sided 95% CI was >0 [57].

LSM change from baseline to 28 weeks in QLS total score was 7.47 ± 1.53 for AOM 400, relative to 2.80 ± 1.62 for paliperidone palmitate; a statistically significant LSM difference between treatments of 4.67 (95% CI 0.32–9.02, $P = 0.036$) confirming the non-inferiority and establishing superiority of AOM 400 over paliperidone palmitate [57]. The variation in QLS from baseline seen with AOM 400 represents a clinically relevant improvement in health-related quality of life and functioning. In pre-defined clinical and treatment effectiveness analyses, AOM 400 was also consistently superior to paliperidone palmitate in younger patients (≤35 years). In this group, the LSM treatment difference from baseline at week 28 favoring AOM 400 was 10.7 (95% CI 0.70–20.7, $P = 0.037$); results which appear to indicate a greater treatment benefit with aripiprazole in younger patients than that seen with paliperidone [57].

Adverse events were the most common reason for patient discontinuation in the study (AOM 400: 11.1%; paliperidone palmitate: 19.7%). Treatment-emergent adverse events (TEAEs) were more frequent with paliperidone palmitate rather than AOM 400. The most frequent TEAEs during the 20-week LAI continuation phase of the study were weight gain, psychotic disorder, and insomnia, all of which occurred more frequently in paliperidone palmitate-treated patients. Extrapyramidal symptoms were uncommon and occurred in less than 5% of patients in each group.

There were also significant improvements in secondary endpoints, including CGI-S scale. Clinical symptoms were significantly more improved at week 28 with AOM 400 compared with paliperidone palmitate (LMS between-treatment difference in change from baseline −0.28, 95% CI −0.48 to −0.09, $P = 0.004$) when assessed with the CGI-S score. This effect was even more pronounced in younger patients (≤35 years) in whom the LMS between-treatment difference in change from baseline in CGI-S was −0.44 (95% CI −0.83 to −0.06, $P = 0.026$) in favor of AOM 400.

Post hoc analyses of data from the QUALIFY study have shown that the superior improvements in health-related quality of life and functioning were accompanied by a reduced risk of sexual dysfunction and lower elevation of prolactin levels with AOM 400, compared with paliperidone palmitate [68]. These effects may be related to the differential activity of aripiprazole and paliperidone on the dopamine D_2 receptor.

Expert Opinion

The prevention of relapse, improving the quality of life and psychosocial functioning of the patient and maintaining recovery are key long-term goals of pharmacological therapy for schizophrenia. Relapse can be distressing for the patient and their caregivers and threatens the patient's ability to live an independent life, increasing the burden of care and the risk of rehospitalization and relative costs. In addition, when relapse is impending or present, rates of substance abuse, suicide and violent behavior rise [2, 7]. Assuring continuity of treatment is key for the prevention of relapse, as almost all

patients with schizophrenia will relapse if antipsychotic therapy is discontinued [19, 26].

Due to its pharmacological profile, aripiprazole represents an innovative therapeutic choice for major psychiatric disorders. Its modulatory properties on different neurotransmitter systems highlight a drug with a broad pharmacological profile and clinical effectiveness in the acute and long-term treatment, as demonstrated in different clinical trials [69].

The LAI formulation of aripiprazole at dose of 400 mg (AOM 400) is effective in reducing the risk of relapse, and it is well tolerated with a safety profile comparable to oral aripiprazole [55, 62]. Because of its specific mechanism of action and as demonstrated in clinical studies, AOM 400 has important effects on both positive and negative symptoms of schizophrenia, so that it provides a valid treatment option for patients with a prevalence or persistence of negative symptoms (with or without cognitive dysfunction), also induced by other antipsychotics (e.g., haloperidol, risperidone and paliperidone) such as decreased ability to initiate tasks, affective blunting, apathy, abulia, lowered levels of motivation or drive and poor social relationships. Based on the clinical experience of the authors, after AOM 400 introduction, an improvement of positive and negative symptoms accompanied by a decrease in episodes of irritability was reported, which allowed the patients to increase social (e.g., interaction with family, active social life, establishment of socio-sexual relationships) and working (e.g., return to work, ready for work, satisfaction with the work) functioning and ameliorate the overall quality of life. All these factors further enhance adherence to treatment.

Of particular importance is the QUALIFY study, which had a more naturalistic study design than traditional pivotal studies, and which used the QLS scale as a primary endpoint to compare the effectiveness of AOM 400 and paliperidone palmitate [57]. As a widely used and validated health-related quality of life measure which focuses on intrapsychic, social and negative symptoms, the QLS is valuable in measuring functioning in schizophrenia, including response to pharmacological therapy [66]. The four domains of QLS, i.e. intrapsychic foundations (e.g., sense of purpose, motivation, curiosity, anhedonia, aimless inactivity, empathy, emotional interaction), interpersonal relationships (e.g., household, friends, acquaintances, social activity and network and initiative, withdrawal, sociosexual), instrumental role (e.g., occupational role, work functioning, work level, and work satisfaction), and commonplace objects and activities (participation in the community) reflect all of the aspects that the clinician evaluates regarding quality of life in the clinical practice and represent a central long-term goal of antipsychotic therapy for clinicians and patients.

In QUALIFY, as well as producing a statistically significant difference in QLS total score relative to paliperidone palmitate, AOM 400 significantly improved the intrapsychic foundations domain of the QLS, which also includes negative symptoms, contributing most to the greater, and clinically relevant, improvement in patient functioning seen with AOM 400, compared with paliperidone palmitate [57]. Based on the clinical experience of the authors, the important positive effect of aripiprazole LAI on clinical symptoms, functioning and health-related quality of life is pivotal in order to involve patients in rehabilitation programs, obtaining long-term continuity.

Furthermore, AOM 400 was particularly effective in younger patients, with a between-treatment difference of 10.7 points in patients aged $\leq$35 years, which is larger than the non-inferiority margin of minus 5 points and approximately double the 5.3-point difference from baseline estimated by Falissard et al. to be the minimal clinically important difference for QLS [67]. Another key secondary endpoint, CGI-S, which showed significant improvements from baseline at study end with AOM 400 relative to paliperidone palmitate, was also greater in younger patients [57].

This evidence supports the benefits of early intervention with LAIs, seen in other studies [14, 21, 70], with early intervention in patients with schizophrenia improving clinical and psychosocial long-term outcomes while, on the other hand, the risk of relapse or poor long-term outcomes increases when access to effective mental health services is delayed. Newly diagnosed

patients may not be fully aware of or have fully accepted the seriousness of their illness, and they are often less adherent, making the use of a long-acting medication a sensible strategy to be considered [24]. Treatment considerations that tend to reserve LAIs for patients in stages of the disease when the symptoms are most severe, when treatment with oral medications fails, or when there are problems of poor adherence should be reexamined. Daily interactions between caregivers and the patient to ensure compliance with oral antipsychotic medications can be negative and stressful. With its demonstrated efficacy and effectiveness and uncertainty about adherence removed, AOM 400 may be of particular benefit for younger patients.

Despite the apparent reluctance of some physicians to offer LAIs, even when the potential benefit to the patient is clear, in the clinical experience of the authors switching to AOM 400 from other LAIs or oral antipsychotics was completely manageable. A discussion of optimal switching strategies to AOM from other antipsychotic agents is beyond the scope of this article. However, strategies for switching have been discussed by recent expert consensus panels [71, 72], and a recent article by Raoufinia et al. [64] provides a rationale and details recommended strategies for the initiation of AOM in patients with schizophrenia. The effects of AOM 400 are apparent from the start of therapy, and rapid amelioration of symptoms was noticed by caregivers and contributed to patient satisfaction with treatment. A recent study that evaluated hospitalization rates in patients switched from oral antipsychotics to AOM 400 [56] found that the number of psychiatric hospitalizations significantly reduced after switching to AOM, further supporting the effectiveness of using AOM in the community setting.

The safety and tolerability of AOM 400 was comparable to previous experience with orally-administered aripiprazole, with minimal weight gain or changes in metabolic parameters and prolactin levels [56]. Administration of AOM 400 is straightforward, with minimal injection site pain and a reduced need for concomitant treatment with other antipsychotic compounds to achieve treatment aims. Patient-reported treatment satisfaction with AOM is high after switching to AOM 400 maintenance therapy, with patients describing positive perceptions of tolerability with no or fewer side effects with AOM 400 than with prior antipsychotic medication [73]. The authors have, in their clinical practice, patients on AOM 400 therapy for over 30 months that have maintained a good quality of life without relapses or rehospitalization. Patient satisfaction with therapy allows patients to return to a productive life with enhanced social relationships and work reintegration. The effective control of symptoms, reduced rates of sexual dysfunction, hyperprolactinemia, metabolic effects, and extrapyramidal symptoms with AOM 400 make it particularly suited for patients with these side effects from other antipsychotic medications.

Taking into account all of the considerations above, the choice of using AOM 400 in clinical practice might be oriented on young patients, who can hence benefit more from a long-acting treatment effective on clinical symptoms, functioning and quality of life, on patients presenting a history of positive and negative symptoms with or without cognitive impairments, and on patients experiencing persistent side effects with the current treatment such as metabolic effects, weight gain, extra-pyramidal symptoms and sexual problems. Nevertheless, the promising results across the "full spectrum" of efficacy in traditional clinical trials, as well as those encompassing the concept of effectiveness in a more naturalistic setting of real-life clinical practice, support the use of AOM 400 beyond situations of poor adherence or when oral antipsychotics have failed. Although further studies are required to fully define the role of AOM 400 in the treatment of schizophrenia, evidence is now available for its use across the continuum of patients encountered in clinical practice.

CONCLUSIONS

Long-acting injectable antipsychotics can play an important role in enhancing adherence, preventing relapse, and reducing hospitalizations in patients with schizophrenia. Evidence

from traditional "explanatory" clinical trials under highly controlled and well-defined conditions, together with that from more "naturalistic" or "pragmatic" studies encompassing the concept of effectiveness in a naturalistic setting more representative of real-life clinical practice, support its early use and suggest a broader role for AOM as a valid long-term treatment option in the treatment of schizophrenia, not just in situations of poor adherence or when oral antipsychotics have failed.

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